REMARKS/ARGUMENTS

Claims 4 and 5 have been amended and claims 6 and 7 have been added to correct for improper multiple dependencies. In addition, the term "transgenic" has been added to the claims. Claim 8 has been added directed to an immunocyte derived from the transgenic animals of claims 1 or 2, support for which may be found particularly on page 8, lines 7-8 and the paragraph spanning pages 14-15 of the specification. Accordingly, no new matter has been added by way of these claim amendments.

Claims 1-7 are currently pending. Reconsideration of these claims is respectfully requested in view of the following remarks. The Examiner's comments in the Office Action are addressed below in the order set forth therein.

The Objection to the Claims Should Be Withdrawn

The Examiner objected to claims 4 and 5 for containing improper multiple dependencies. Claims 4 and 5 have been amended as described above. Accordingly, Applicants request that this objection be withdrawn.

The Rejections of the Claims Under 35 U.S.C. §101 Should Be Withdrawn

The Examiner has rejected claims 1-3 under 35 U.S.C. §101 because "the skilled artisan would not find any of the asserted utilities of the non-human animals to be specific and substantial, or well-established" (page 5 of the Office Action dated November 1, 2007). This rejection is traversed for the reasons provided below.

Applicants submit that the Examiner has incorrectly applied the requirements of 35 U.S.C. § 101 to the present claims. It is not Applicants' burden to establish utility unless the Examiner shifts the burden by establishing, with evidence, that one of skill in the art would doubt the asserted utility. *In re Brana*, 51 F.3d 1560, 1565 (Fed. Cir. 1995) (holding that "[o]nly after the PTO provides evidence showing that one of ordinary skill in the art would reasonably doubt the asserted utility does the burden shift to the Applicant to provide rebuttal evidence sufficient to convince such a person of the invention's asserted utility"). As the Utility Examination Guidelines make clear, "[w]here the asserted utility is not specific or substantial, a *prima facie*

showing [of no specific and substantial credible utility] must establish that it is more likely than not that a person of ordinary skill in the art would not consider that any utility asserted by the applicant would be specific and substantial. The *prima facie* showing must contain the following elements: (1) An explanation that clearly sets forth the reasoning used in concluding that the asserted utility for the claimed invention is not both specific and substantial nor well-established; (2) Support for factual findings relied upon in reaching this conclusion; and (3) An evaluation of all relevant evidence of record, including utilities taught in the closest prior art." 66 Fed. Reg. 1098 (2001).

The Examiner states that one of two asserted utilities in the specification is "the use of the non-human animals or cells derived therefrom to identify substances that promote or suppress the responses to TLR4 ligands (specification, page 14, 3rd parag. to page 15, 1st parag.)" (page 4 of the Office Action dated November 1, 2007). The Examiner concludes that "[i]n regards to asserted utility 2) ... the specification fails to demonstrate that mice with a homozygous disruption of an endogenous TRAM gene have any phenotype associated with any disease, or can in fact be used as a model for any particular disease" (page 5 of the Office Action dated November 1, 2007). Furthermore, the Examiner states that "the specification does not teach what distinguishes the claimed non-human animals from wild-type non-human animals in screens for medicaments that prevent or treat bacterial infections" (page 5 of the Office Action dated November 1, 2007). Applicants disagree.

Applicants direct the Examiner's attention to the following passage excerpted from the specification, which describes in detail the phenotype of the TRAM-deficient mice of the invention:

> TRAM-deficient mice showed severe defects in cytokine production, splenocyte proliferation and up-regulation of surface molecules, in response to the TLR4 ligands, but not to other TLR ligands. Furthermore, TLR4-mediated, but not TLR3-mediated, expression of IFN-β and IFN-inducible genes was inhibited in TRAM-deficient mice. In intracellular signaling, LPS-induced autophosphorylation of IRAK-1 and the early phase of NF-κB activation were intact in TRAM-deficient mice. However, no activation of IRF-3 was observed while a defect in the late phase of NF-κB activation in response to LPS, but not to poly (I:C), was

observed in TRAM-deficient cells. Given that the latter event is a feature of the MyD88-independent signaling pathway, it was indicated that TRAM specifically mediates the MyD88-independent pathway of TLR4 signaling.

In TRAM-deficient mice, TLR4-mediated activation of the MyD88-dependent pathway, which is characterized by autophosphorylation of IRAK-1 and the early phase of NF-κB activation, was comparable to that of wild-type cells. However, TLR4-mediated production of proinflammatory cytokines was reduced. Similarly, TLR4-mediated production of proinflammatory cytokines was significantly reduced in mice lacking TRIF, which is essential for TLR4- and TLR3-mediated MyD88-independent pathways. As MyD88-deficient mice showed similar phenotype, activation of the MyD88-independent pathway is clearly required for induction of proinflammatory cytokines (e.g., see Science 301, 640-643, 2003, Identification of Lps2 as a key transducer of MyD88-independent TIR signaling; Nature, 424, 743-748, 2003). Therefore, in TLR4 signaling, activation of both MyD88-dependent and MyD88-independent (TRAM/TRIF-dependent) pathways is required for proinflammatory cytokine production. However, in signaling pathways of TLR2, TLR5 and TLR9, none of which activate the MyD88-independent pathway, only the activation of MyD88-dependent pathway is sufficient to induce proinflammatory cytokines (e.g., see Science 282, 2085-2088, 1998; Nat. Immunol. 3, 392-398, 2002; J. Exp. Med. 192, 595-600, 2000; Curr. Biol. 10, 1139-1142, 2000). Therefore, at present, it remains unclear why TLR4 signaling requires activation of both MyD88-dependent and TRIF-dependent pathways to induce proinflammatory cytokines. However, it has become clear that only TLR4 utilizes all of the presently characterized TIR domain-containing adaptors, that is, MyD88, TIRAP, TRIF and TRAM.

As described above, TRAM-deficient mice showed normal responses to ligands for TLR2, TLR7, TLR9 and IL-1β, but severely defective MyD88-dependent responses to the ligands recognized by TLR4. Furthermore, activation of the TLR4-mediated MyD88-independent, but not MyD88-dependent, signaling cascade was abolished in TRAM-deficient mice. Although this phenotype was reminiscent of that of TRIF-deficient mice which lack activation of MyD88-independent pathway in both TLR3 and TLR4 signaling, TRAM-deficient mice showed a normal response to TLR3 ligands. These results indicate that TRAM is an adaptor molecule that provides specificity for the

MyD88-independent pathway of TLR4 signaling.

See pages 5 to 7 of the specification (emphasis added). Accordingly, the specification clearly describes that TRAM-deficient mice showed severe defects in cytokine production, splenocyte proliferation and up-regulation of surface molecules in response to the TLR4 ligands, but not to other TLR ligands, and that TLR4-mediated expression of IFN-β and IFN-inducible genes was inhibited in TRAM-deficient mice.

The USPTO's Utility Examination Guidelines state that "[a] patent examiner must accept a utility asserted by an applicant unless the Office has evidence or sound scientific reasoning to rebut the assertion. The examiner's decision must be supported by a preponderance of all the evidence on record. *In re Oetiker*, 977 F.2d 1443, 1445, 24 USPQ2d 1443, 1444 (Fed. Cir. 1992)." 66 Fed. Reg. 1096 (2001). The Guidelines make a similar point several pages later, stating that "Office personnel are reminded that they must treat as true a statement of fact made by an applicant in relation to an asserted utility, unless countervailing evidence can be provided that shows that one of ordinary skill in the art would have a legitimate basis to doubt the credibility of such a statement." 66 Fed. Reg. 1098-99 (2001). However, here the Examiner has not provided any evidence that one of skill in the art would doubt this asserted utility, and instead has ignored statements in the specification that support Applicants' assertions.

In view of the above discussion, Applicants respectfully submit that the Examiner has incorrectly applied the requirements of 35 U.S.C. §101 to the pending claims. Therefore, Applicants request that this rejection be withdrawn.

The Examiner has also rejected claims 1-3 under 35 U.S.C. §101 for encompassing natural mutations. As described above, the claims have been amended to include the term "transgenic", as suggested by the Examiner. Accordingly, Applicants submit that this rejection has been obviated and request that it be withdrawn.

The Rejection of the Claims Under 35 U.S.C. §112, First Paragraph, Should Be Withdrawn

The Examiner has rejected claims 1-3 under 35 U.S.C. §112, First Paragraph, as failing to comply with the enablement requirement. This rejection is traversed for the reasons provided

below.

The Examiner states that "the claimed non-human animals do not exhibit any phenotype related to any disease or disorder and thus, the use of the claimed non-human animals for reasons other than as a model of disease is not readily apparent" (page 7 of the Office Action dated November 1, 2007). The Examiner also states that "while the specification indicates that the claimed non-human animals can be used as screens for substances that promote the response to ligands recognized by LTR4, such that the substances can possibly be used in prevention or treatment of bacterial infections, nothing in the specification indicates what phenotype the claimed non-human animals have over that of wild-type animals" (pages 7-8 of the Office Action dated November 1, 2007). Applicants disagree.

As described in detail above, the specification clearly describes that TRAM-deficient mice showed severe defects in cytokine production, splenocyte proliferation and up-regulation of surface molecules in response to the TLR4 ligands, and that TLR4-mediated expression of IFN-β and IFN-inducible genes was inhibited in TRAM-deficient mice (See pages 5 to 7 of the specification). Furthermore, the experimental examples provide ample direction to one of skill in the art as to how to generate TRAM-deficient mice and how to test for defects in cytokine production, splenocyte proliferation, and up-regulation of surface molecules in response to TLR4 ligands, as well as how to test for inhibition of TLR4-mediated expression of IFN-β and IFN-inducible genes. Applicants believe that in view of such teachings in the specification, one of skill in the art would realize that the claimed invention was useful and would also know how to make and use the claimed invention.

For these reasons, the Examiner has not shown that the claimed invention fails to meet the requirements of 35 U.S.C. §112, First Paragraph. Therefore, Applicants respectfully request that this rejection be withdrawn.

CONCLUSION

In view of the aforementioned remarks, Applicants respectfully submit that the rejections of the claims under 35 U.S.C. §§101 and 112, First Paragraph, are overcome. Accordingly, Applicants submit that this application is now in condition for allowance. Early notice to this effect is solicited.

It is not believed that extensions of time or fees for net addition of claims are required, beyond those that may otherwise be provided for in documents accompanying this paper. However, in the event that additional extensions of time are necessary to allow consideration of this paper, such extensions are hereby petitioned under 37 CFR § 1.136(a), and any fee required therefore (including fees for net addition of claims) is hereby authorized to be charged to Deposit Account No. 16-0605.

Respectfully submitted,

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